Assessment of mitochondrial function measurements in Parkinson's disease patients and healthy volunteers to identify new potential biomarkers.

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The primary goal of this phase 0 study is to assess the variability of mitochondrial function measurements in healthy volunteers and PD patients.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Movement disorders (incl parkinsonism)
Study type	Observational invasive

Summary

ID

NL-OMON56963

Source
ToetsingOnline

Brief title
Mitochondrial function measurements in Parkinson*s disease patients

Condition

- Movement disorders (incl parkinsonism)

Synonym
Parkinson's disease

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: Lucy Therapeutics,CHDR en Lucy

therapeutics

Intervention

Keyword: Biomarker, GBA-mutations, Mitochondrial function, Parkinson's disease

Outcome measures

Primary outcome

Characterize day-to-day, intra-individual and inter-individual variability of mitochondrial function in the brain measured with 31-P MRS of early onset PD patients, late onset PD patients, GBA mutation PD patients and healthy volunteers.

Secondary outcome

Characterize day-to-day, intra-individual and inter-individual variability of mitochondrial function measured in peripheral blood mononuclear cells or whole blood of early onset Parkinson*s disease patients, late onset Parkinson*s disease patients, GBA mutation Parkinson*s disease patients and healthy volunteers.

Characterize day-to-day and inter-individual variability of circulating biomarkers in plasma in idiopathic early onset Parkinson*s disease patients, idiopathic late onset Parkinson*s disease patients, GBA mutation Parkinson*s disease patients and healthy volunteers.

Characterize day-to-day, intra-individual and inter-individual variability of mitochondrial function in the skin of early onset Parkinson*s disease patients, late onset Parkinson*s disease patients, GBA mutation Parkinson*s disease

patients and healthy volunteers.

Study description

Background summary

Parkinson's disease (PD) is a progressive, neurodegenerative disorder of aging that affects both motor and cognitive function. The core pathology of Parkinson*s is degeneration of the dopaminergic neurons in the midbrain (substantia nigra pars compacta) leading to a dopamine deficit in the striatum. The dysregulation in this dopamine circuit leads to the development of motor symptoms, as well as non-motor symptoms such as autonomic dysfunction, sleep disturbance, depression, **********gastrointestinal dysfunction, incontinence and cognitive impairment. In late-onset idiopathic PD and dominantly inherited genetic variants, the degeneration of neurons occurs in association with the formation of intraneuronal Lewy inclusion bodies.

Insight into the function and dysfunction of PD-associated gene products helped to elucidate the underlying mechanisms leading to neuronal cell death. Accumulating evidence indicated that PD-associated genes directly or indirectly affect mitochondrial function *(Grünewald et al., 2019)*. Different aspects of mitochondrial function seem to be affected, including membrane potential, production of reactive oxygen species (ROS), import defects, dysfunction of electron transport chain (ETC) complexes, adenosine triphosphate (ATP) levels and imbalances in Ca+ homeostasis.

Therefore, improvement of mitochondrial function provides important targets for new therapeutic agents for PD patients. In order to assess efficacy and target engagement of these therapeutic agents, suitable biomarkers need to be available. There are different ways to assess mitochondrial function, 31-phosphorus Magnetic Resonance Spectroscopy (31P-MRS) is a way to asses mitochondrial function in vivo *(van Diemen et al., 2021)*. Inclusion of a visual stimulus in 31P-MRS studies has shown specific differences between patients with PD and healthy control subjects, particularly in the recovery phase after stimulation *(Rango et al., 2006, 2020)*. Flow-mediated skin fluorescence (FMSF) provides a non-invasive method to assess mitochondrial function and has recently been used to demonstrated differences in patients with primary mitochondrial disease *(van Kraaij et al., 2023)*. In addition, mitochondrial dysfunction could be assessed via circulating biomarkers or by assessing mitochondrial function in whole blood and peripheral blood mononuclear cells (PBMCs**********) **********(van Kraaij et al., 2023)*.

Study objective

The primary goal of this phase 0 study is to assess the variability of mitochondrial function measurements in healthy volunteers and PD patients.

Study design

A non-interventional phase 0, method validation study to assess day-to-day, inter-individual and intra-individual variability of biomarker measurements. Participants will visit Centre for Human Drug Research (CHDR) on day 1 and 7 (up to day 28). On each day mitochondrial function measurements will be performed.

Study burden and risks

This is a non-interventional biomarker study. No investigational drug will be administered. Biomarkers will be assessed using 31P-MRS or via blood sampling. All blood collections will be performed at the clinical research unit and will be medically supervised by qualified medical staff. 31P-MRS will be performed in the university medical center by qualified staff. The blood sampling, flow mediated skin fluorescence and the 31P-MRS are considered low-risk procedures and the burden for the participants related to the study procedures will be kept to a minimum.

Contacts

Public
Centre for Human Drug Research

Zernikedreef 8
Leiden 2333CL
NL
Scientific
Centre for Human Drug Research

Zernikedreef 8
Leiden 2333CL
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Healthy volunteers:
1. Adult male or female subjects 50 years of age or older, inclusive.
2. Healthy status as defined by absence of evidence of any significant active acute or chronic disease or illness following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, haematology, blood chemistry and urinalysis, as judged by the investigator,
3. Body mass index (BMI) between 18-32 kg/m2, inclusive.
4. Evidence of a personally signed and witnessed informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
5. Women of childbearing potential must use an effective form of contraception (e.g., oral contraceptive, condom use, intrauterine device (IUD), abstinence of heterosexual intercourse) during the study.

Parkinsons disease patients:
6. Adult male or female subjects 50 years of age or older, inclusive, with a confirmed diagnosis of Parkinson*s disease (Hoehn and Yahr grade 1-3).
7. Healthy status as defined by absence of evidence of any significant active acute or chronic disease or illness following (apart from Parkinson*s disease) a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, haematology, blood chemistry and urinalysis, as judged by the investigator.
8. BMI between 18-32 kg/m2, inclusive.
9. Evidence of a personally signed and witnessed informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
10. Women of childbearing potential must use an effective form of contraception (e.g., oral contraceptive, condom use, IUD, abstinence of heterosexual intercourse) during the study.

Exclusion criteria

Healthy subjects
1. Legal incapacity or inability to understand or comply with the requirements of the study

2. Clinically significant findings as determined by medical history taking, physical examination, ECG, laboratory findings and vital signs
3. Female participant is pregnant or planning to become pregnant during the study.
4. Have a urine drug screen detecting illicit drug(s) of abuse (morphine, benzodiazepines, cocaine, amphetamine, THC) or positive alcohol breath test at screening. A positive urine drug screen for prescribed medication is allowed at the discretion of the investigator.
5. Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening
6. Consume, on average, >8 units/day of (methyl)xanthines (e.g., coffee, tea, cola, chocolate) and not able to refrain from use during each stay at the CHDR clinic
7. History or clinical evidence of drug abuse
8. History (within 3 months of screening) of alcohol consumption exceeding 2 standard drinks per day on average. Unwillingness or inability to refrain from alcohol consumption at least 24 hours before screening and before each scheduled visit.
9. Smoking of >5 cigarettes/day or equivalent and unwillingness or inability to refrain from tobacco usage within 12 hours before each visit until the end of that visit.
10. Loss of blood >= 500 ml within 3 months before screening
11. Presence of any contraindication to have magnetic resonance imaging (MRI) scans with checkerboard stimulus performed (e.g. claustrophobia, pacemaker, intracranial clips, deep brain stimulation, photosensitive epilepsy etc.).
12. Participation in a clinical trial including an investigational medicinal product within 90 days of screening or more than 4 times within a year.
13. A visual acuity below -10 or above +10
14. Not being able to lay still and flat on back for 30-60 minutes.

Parkinsons disease patients
15. Legal incapacity or inability to understand or comply with the requirements of the study
16. Any known PD-related gene mutations, except for GBA mutation.
17. Reside in a nursing home or assisted care facility
18. Clinically significant findings as determined by medical history taking, physical examination, ECG, laboratory findings and vital signs, other than Parkinson*s disease
19. Any current, clinically significant, known medical condition other than Parkinson*s disease. Patients with a diagnosis of neurological diseases, other than Parkinson*s disease, including Alzheimer*s disease, Huntington*s disease, vascular dementia, progressive supranuclear gaze palsy, multiple system atrophy, drug-induced parkinsonism, essential tremor, primary dystonia, epilepsy, etc., that are considered clinically relevant by the investigator
20. Female participant is pregnant or planning to become pregnant during the study.
21. Have a urine drug screen detecting illicit drug(s) of abuse (morphine,

benzodiazepines, cocaine, amphetamine, THC) or positive alcohol breath test at screening. A positive urine drug screen for prescribed medication is allowed at the discretion of the investigator.
22. Positive HBsAg, HCV Ab, or HIV Ab at screening
23. Consume, on average, >8 units/day of (methyl)xanthines (e.g., coffee, tea, cola, chocolate) and not able to refrain from use during each stay at the CHDR clinic
24. History or clinical evidence of drug abuse
25. History (within 3 months of screening) of alcohol consumption exceeding 2 standard drinks per day on average. Unwillingness or inability to refrain from alcohol consumption at least 24 hours before screening and before each scheduled visit.
26. Smoking of >5 cigarettes/day or equivalent and unwillingness or inability to refrain from tobacco usage within 12 hours before each visit until the end of that visit.
27. Loss of blood >= 500 ml within 3 months before screening, including plasma donation.
28. Presence of any contraindication to have MRI scans with checkerboard stimulus performed (e.g. claustrophobia, pacemaker, intracranial clips, deep brain stimulation, photosensitive epilepsy etc.).
29. Participation in a clinical trial including an investigational medicinal product within 90 days of screening or more than 4 times within a year.
30. A visual acuity below -10 or above +10
31. Not being able to lay still and flat on back for 30-60 minutes.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	29-10-2024
Enrollment:	32
Type:	Actual

Ethics review

Approved WMO Date:	14-08-2024
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-01-2025
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL86774.056.24